

REPEATED POST- OR PRESESSION COCAINE ADMINISTRATION:
ROLES OF DOSE AND FIXED-RATIO SCHEDULE

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Effects of repeated administration of cocaine to animals behaving under operant contingencies have depended on when the drug is given. Moderate doses given pre-session have generally led to a decrease in the drug's effect, an outcome usually referred to as tolerance. When these same doses have been given after sessions, the usual result has been no change or an increase in the drug's effects, with the latter usually referred to as sensitization. In the present study, repeated post-session administration of a relatively small dose of cocaine (3.0 or 5.6 mg/kg) to pigeons responding under a multiple fixed-ratio 5, fixed-ratio 100 schedule of food presentation generally resulted in tolerance to the rate-decreasing effects of the drug. When the same dose was given before sessions, little additional tolerance was observed, although some subjects showed further tolerance in the small-ratio component. A regimen of repeated post-session injection of larger (10.0–23.0 mg/kg) doses suppressed key pecking during the session; responding resumed following discontinuation of post-session administrations. Effects of post-session administration of cocaine, therefore, depended on the dose, with smaller doses leading to tolerance and larger ones to suppression of behavior during the session. Effects of post-session drug administration of either small or large doses were not related to whether effects of post-session drug were experienced mainly in the operant test chamber or in the pigeon's home cage. The results with large post-session doses are compatible with a view that the drug acted as a Pavlovian unconditional stimulus, with the session-related stimuli acting as a long-duration Pavlovian conditional stimulus. Tolerance following post-session administration of the smaller doses challenges the view that it depended on experiencing the drug's effects while the arranged reinforcement contingencies were in effect.

Key words: cocaine, tolerance, contingent tolerance, Pavlovian conditioning, conditional-stimulus duration, key peck, pigeons

Effects of repeated exposure to cocaine have varied. In some studies, effects of the drug have increased—a phenomenon generally called sensitization (e.g., Downs & Eddy, 1932a, 1932b; Post & Rose, 1976; Stewart & Badiani, 1993). In others, effects have decreased—an outcome usually labeled tolerance (e.g., Mercier & Dessaigne, 1960; Moore & Thompson, 1978). Although the variables responsible for these two classes of outcomes have not been fully delineated, it is clear that behavioral processes can play a role, both in the development of sensitization (cf. Post, Weiss, Fontana, & Pert, 1992) and of tolerance (cf. Wolgin, 1989).

An important conceptualization of how behavioral factors can enter into the development of drug tolerance emanated from a line of research initiated by Chen (1968). In his

work, one group of rats received ethanol before behavioral test sessions in a circular maze, whereas another group received the drug after each session. With his procedure, sometimes called the Before-After, or B-A, procedure, Chen found that tolerance to ethanol's effects on maze performance developed only in the rats that received the drug before sessions, despite the fact that all rats had received equivalent exposure to ethanol. Many subsequent experiments with the B-A procedure, using both ethanol and other psychoactive drugs, have shown a similar outcome: subjects receiving drugs before the test session become tolerant, whereas those receiving drug after sessions do not (Wolgin, 1989). Tolerance that depends on pre-session drug administration is usually called "contingent tolerance" (Carlton & Wolgin, 1971) to contrast it with tolerance that results simply from repeated drug exposure (sometimes called pharmacological tolerance).

Woolverton, Kandel, and Schuster (1978) were the first to examine cocaine's effects in the B-A design, and they found that rats that received cocaine repeatedly before daily ses-

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sions in which they drank milk became tolerant to the drug's intake-reducing effects whereas those that received an equivalent regimen of postsession cocaine did not. Other investigations with rats (e.g., Smith, 1990) and also primates (e.g., Branch & Sizemore, 1988) also have revealed contingent tolerance to effects of cocaine.

The most common account of contingent tolerance is based on hypothesized behavioral adjustments that develop during repeated drug exposure (see Wolgin, 1989). In this view, the drug produces novel patterns of behavior that interact with the arranged reinforcement contingencies. Specifically, these interactions are presumed to result in the reinforcement of behavior that compensates for the drug-induced changes such that losses in reinforcement are counteracted (Schuster, Dockens, & Woods, 1966).

Research by Smith (1986) with amphetamine revealed how behavioral parameters can interact with repeated drug exposure. In his study, rats pressed a lever under a two-component multiple schedule of food presentation. One component was a differential-reinforcement-of-low-rate (DRL) schedule; the other was a random-ratio (RR) schedule. Smith repeatedly administered a dose of amphetamine that decreased RR rate and increased DRL rate, thus reducing reinforcement rate in both components. Tolerance developed in the RR component but not in the DRL component. When he subsequently removed the RR component, tolerance materialized in the DRL component. Smith noted that baseline rate of reinforcement was higher in the RR component, so he suggested that tolerance developed in the DRL component only when it was isolated because gains in reinforcement rate afforded by tolerance in the DRL component were eclipsed by those that occurred in the RR component when it was available.

Similar differential tolerance development to effects of cocaine has been reported by Hoffman, Branch, and Sizemore (1987), Hughes and Branch (1991), Nickel, Alling, and Poling (1993), and van Haaren and Anderson (1994). In those experiments, multiple schedules with differently valued fixed-ratio (FR) schedules were employed, and tolerance development was generally limited to behavior controlled by smaller FR values.

That is, as in Smith's (1986) study, tolerance was more pronounced in the component with the higher baseline rate of reinforcement.

The present study extends these prior findings with repeated cocaine administration under multiple FR schedules in three ways. First, to assess the degree to which any tolerance observed was an instance of contingent tolerance, we compared effects of pre-session drug administration with postsession administration. Second, we examined the effects of repeated administration of two different doses of cocaine. Previous research with cocaine has indicated that dose of drug given repeatedly pre-session is an important determinant of the outcome (e.g., Bowen, Fowler, & Kallman, 1993; Branch, Wilhelm, & Pinkston, 2000; Stafford & Branch, 1996.) Smaller doses often lead to tolerance, whereas larger doses frequently do not. In the present study, we examined whether similar dose effects occur when cocaine is repeatedly administered post-session. Third, the present experiments were designed to examine the possibility that tolerance to cocaine's effects on performance maintained under multiple FR schedules might also be influenced by Pavlovian factors. Pavlovian conditioning has been implicated as a second type of behavioral process involved in drug tolerance (e.g., Adams, Yeh, Woods, & Mitchell, 1969; Siegel, 1978). The drug is conceptualized as an unconditional stimulus (US) that elicits unconditional responses (UR). When drug is experienced repeatedly in a particular context, that context is posited to serve as a conditional stimulus (CS) that elicits a conditional response (CR) that is opposite of the UR, thus competing with the drug effect (for a review, see Siegel, Baptista, Kim, McDonald, & Weise-Kelly, 2000). In an attempt to assess effects of pairing cocaine's action with the test environment, post-session injections were followed either by a return to the conditioning chamber for the duration of the peak action of the drug or to the home cage.

METHOD

Subjects

Eight experimentally naive White Carneau pigeons served. Each was maintained at approximately 80% of its free-feeding weight by

providing postsession feeding as necessary. Weights of individual pigeons are listed in Table 1. Between sessions, subjects were housed individually in a temperature- and humidity-controlled colony room with a 16:8 hr light/dark cycle. Water and grit were continuously available in the home cage.

Apparatus

Two BRS/LVE pigeon chambers (Model 9381-D) were used. The inside dimensions of the chambers were 35 cm by 31 cm by 35 cm. One wall held three horizontally aligned, translucent plastic response keys. The keys were 2.5 cm in diameter and centered 8 cm from the ceiling. Only the center key was used, and it could be transilluminated by 1.1-W lamps that provided white, red, or green illumination. Each peck with a force of at least 0.15 N was counted as a response and produced 30-ms operation of a Mallory Sonalert® (2900 Hz tone). A 1.1-W lamp (house-light) 2 cm from the top center of the wall provided general illumination. A 6 cm by 4 cm opening was located 8.5 cm below the center key, and mixed grain could be made available through it via operation of a solenoid-operated feeder. During each 3-s feeder operation the aperture was illuminated by a 1.1-W lamp, and all other lights in the chamber were extinguished. To mask extraneous sounds, white noise at 95 dB was present in the room in which the chambers resided. Programming and recording of experimental events were accomplished by a computer system (Palya & Walter, 1993).

Procedure

Training and baseline conditions. Throughout the study, sessions were conducted 7 days per week at about the same time of day for each subject. Sessions were preceded by a 5-min blackout in which no stimuli were presented and no contingencies were arranged. Key pecking was established using an autoshaping (cf. Brown & Jenkins, 1968) procedure. Presentations of grain, each preceded by 8-s illumination of the key by white light, occurred on a variable-time 60-s schedule. Sessions lasted for 50 food presentations. The first peck to the lighted key resulted in immediate presentation of grain. The key was then continuously illuminated, and each peck produced immediate access to food until 50 pecks had

occurred. Autoshaping lasted from 5 to 12 sessions across pigeons.

Next, sessions began with the key illuminated red. Initially, each peck resulted in access to grain. After four grain deliveries, the ratio of pecks to food presentations was increased to 2. Subsequently, the ratio was increased to 4, 8, 11, 16, 20, 25, 30, 35, 40, 45, 50, 60, 70, 85, and 100. The criterion for increasing the ratio was that every interresponse time in the ratio had to be less than 1 s for four consecutive ratios. Sessions ended after 30 grain presentations, and the ratio at the beginning of a session was the value achieved at the end of the preceding session. For Pigeon 91, the sequence of ratios was modified after FR 70 because of relatively low and erratic rates of responding at larger ratios. For this pigeon, the final ratio was FR 75.

The final schedule arrangement was then introduced. It consisted of a multiple FR 100 FR 5 schedule. Each session began with the key illuminated red (FR 100 component; FR 75 for Pigeon 91). After four grain presentations, a 30-s intercomponent interval with all lights out was presented. The key then was lit green (FR 5 component) for the next four grain presentations, after which the intercomponent interval ensued. This continued until each component had occurred three times. To ensure exposure to both components of the multiple schedule when response rates were low, time limits were in effect in each component. They were 25 min for the FR-100 component and 5 min for the FR-5 component. If the time limit expired, the intercomponent interval commenced automatically.

Once daily response rates were considered stable (i.e., showed no systematic session-to-session variation over at least a 10-session span, as judged by visual inspection), an additional 30 sessions were conducted before drug testing began. The total number of sessions of exposure to the final multiple schedule before drug testing began ranged from 45 to 65 across pigeons.

Drugs and injection procedures. Cocaine hydrochloride, obtained from the National Institute on Drug Abuse, was dissolved in 0.9% sodium chloride solution, which served as the vehicle. Doses were determined as the salt, and injections were made into the breast muscle in a volume of 1.0 ml/kg. When two

Table 1
Conditions and numbers of sessions for each pigeon.

Order	Pigeon			
	33(464g)	521(519g)	32(470g)	586(488g)
1	*Large (5.6) ^a Post(C) ^b - 116 ^c	*Small (5.6) Post(H) - 130	*Small (5.6) Post(C) - 158	*Small (5.6) Post(H) - 162
2	Saline(C) - 55	*Small (5.6) Pre(H) - 152	Large (10) Post(C) - 77	*Small (5.6) Pre(H) - 207
3	Large (5.6) Post(H) - 55	Saline(C) - 116	Saline(C) - 60	Saline(H) - 18
4	Saline(H) - 80	Large (10) Post(C) - 50	Large (10) Post(H) - 25	Large(23) Post(H) - 30
5	Saline(C) - 15	Saline(C) - 20	Saline(H) - 28	Saline(H) - 28
6	Large (5.6) Post(C) - 25	Large (10) Post(H) - 120	Large (10) Post(H) - 38	Saline(C) - 10
7	Saline(C) - 30	Saline(H) - 25	*Saline(H) - 148	Large(23) Post(C) - 55
8	Saline(H) - 30	Saline(C) - 38	Saline(C) - 15	Saline(C) - 38
9	Large (5.6) Post(H) - 35	Large (10) Post(C) - 44	*Small (5.6) Pre(C) - 164	
10	*Saline(H) - 113	Saline(C) - 15		
11	*Saline (3) Post(C) - 137			
12	*Small (3) Pre(C) - 152			

^a Dose in mg/kg.

^b Postsession condition; C = Chamber, H = Home cage.

^c Number of sessions in the condition.

* Dose-response effects assessed.

injections per day were scheduled, the first alternated daily between the left and right breast; the second was into the opposing breast. When testing pre-session drug administration, cocaine injections occurred immediately before placing pigeons in the experimental chamber. When testing post-session drug administration, injections occurred approximately 20 min after session termination. Immediately after each session, pigeons were placed for 20 min in a wire-mesh holding cage that was situated in a room adjacent to that in which sessions were conducted. All post-session injections occurred at the end of the 20-min period. After the injection, a pigeon was either returned to its home cage (home-cage condition) and fed if needed, or it was returned to the conditioning chamber for 40 min (chamber condition). During this time, the chamber's houselight was illuminated, but the key was not, and pecks had no scheduled consequences. At the end of the 40 min, the houselight was extinguished, and the pigeon was returned to its home cage and fed if needed.

Dose-effect determinations. Various doses of cocaine were administered before sessions once per week. The doses initially examined were 0 (Saline), 10.0, 5.6, 3.0, and 1.0 mg/kg, in that order. The sequence was then repeated. After these determinations, these and other doses were sometimes tested in an irregular order. This method of assessing dose-

effect curves was designed to allow evaluation of their stability. Giving doses in two successive fixed sequences and then retesting some doses permitted observation of any systematic changes over the 10 to 21 weeks (i.e., 70 to 147 sessions) needed to complete determination of effects. No such trends were observed for any subject.

Repeated drug-administration procedures. Three dosing conditions were studied in assessing the effects of repeated cocaine administrations: (a) "small" drug dose repeatedly administered post-session, (b) small drug dose repeatedly administered pre-session, and (c) "large" drug dose repeatedly administered post-session. Different pigeons experienced the three conditions in different orders. A condition continued until day-to-day performance was considered stable for 10 or more sessions.

When a small dose of cocaine was given post-session, 4 pigeons were studied in the home-cage condition and 3 in the chamber condition. Each session was preceded by a saline injection and followed by an injection of cocaine (at the end of the 20-min holding period). Designation of the dose as small indicated that it did not substantially suppress behavior when administered acutely, and more importantly, did not result in elimination of pecking when it was given repeatedly post-session. Table 1 shows where in the order of experimentation this condition occurred

Table 1
(Extended)

Pigeon			
562(334g)	393(431g)	91(483g)	57(454g)
*Small (5.6) Post(H) - 184	Large (10) Post(C) - 95	*Large (10) Post(C) - 95	*Small (5.6) Post(H) - 138
*Small (5.6) Pre(H) - 215	Saline(C) - 40	Saline(C) - 105	Small (5.6) Pre(H) - 8
Saline (H) - 60	Saline (H) - 52		
Large (17) Post(H) - 25	Large (10) Post(H) - 36		
Saline(H) - 35	Saline(H) - 53		
Saline(C) - 16	*Saline(C) - 30		
Large (17) Post(C) - 44	*Small (5.6) Post(C) - 181		
Saline(C) - 20	*Small (5.6) Pre(C) - 170		

for each pigeon, the number of sessions in each condition, and whether the animal was returned to its home cage or to the chamber after each session.

When pigeons received the relatively small dose before each session, 3 were tested in the home-cage condition and 3 in the chamber condition. Saline was given at the end of the 20-min holding period. For each pigeon, the same dose that had been identified previously as small for examination of postsession effects was given before each session. Pigeon 57 became ill after 8 days of exposure to pre-session cocaine and was removed from the study.

Dose-response functions were reassessed once exposure to pre- or postsession administration of the smaller dose had led to stable session-to-session performance. This was accomplished by substituting a pre-session injection of cocaine for the daily dose once per week. Tests with additional doses did not begin until at least 60 sessions of daily administration had passed and performance was judged stable. The same method of determining the dose-response function that had been used to assess acute effects was employed.

The numbers of times each dose was tested in each condition are shown in Table 2. To calculate mean values for effects of the repeatedly administered (chronic) dose when a small dose was given before every session, instead of taking data from all the sessions preceded by this dose, we used the data from sessions that occurred the day before tests with other doses or with saline. We judged that these sessions provided a representative

sample of performance under the chronic dose. That is why in Table 2, for the small-before conditions, the listed numbers of "observations" are relatively large for one of the doses for each pigeon. That dose was the chronic dose. Similarly, in calculating a mean value for sessions preceded by injections of saline in the small-after conditions, we used data from sessions that occurred the day before tests with doses of cocaine. That is why the listings in Table 2 of numbers of observations of effects following saline (dose of 0) are relatively large in the small-after conditions.

When an injection of a relatively large dose of cocaine followed each session (at the end of the 20-min holding period), an injection of saline preceded each session. Large doses were initially identified as the smallest that acutely decreased substantially or eliminated pecking during the session. An exception was Pigeon 586. For this subject, 23 mg/kg was finally selected as the large dose after tests with 10 and 17 mg/kg failed to produce results consistent with those of the remaining subjects. Doses eventually classified as large typically resulted in the suppression of pecking when administered repeatedly postsession (see results). That is, they were classified as large based on the outcome of experiments with postsession dosing.

Following every case in which a large dose was administered after sessions, the next phase consisted of administering saline in both daily injections. As noted in Table 1, 6 of the 8 subjects were exposed to both the

Table 2
Number of observations for each dose during dose-effect assessments.

Pigeon	Condition	Dose (mg/kg)							
		0	1.0	3.0	5.6	10	17	23	30
32	Acute	4	3	3	3	3	—	—	—
	Small-After	12	2	2	3	3	2	—	—
	Saline ^a	10	2	2	2	2	2	—	—
	Small-Before	2	2	2	12	3	3	—	—
33	Acute	4	2	2	2	2	—	—	—
	Large-After	9	2	2	2	3	—	—	—
	Saline	8	2	2	2	2	—	—	—
	Small-After	8	2	2	2	2	—	—	—
57	Small-Before	3	2	13	2	6	—	—	—
	Acute	4	3	3	2	2	—	—	—
91	Small-After	11	2	3	2	2	2	—	—
	Acute	2	2	3	5	4	—	—	—
393	Large-After	4	1	1	1	1	—	—	—
	Acute	4	2	2	2	4	2	—	2
	Large-After	5	1	1	1	1	1	—	—
	Saline	14	2	2	3	2	3	—	2
521	Small-After	2	3	2	3	2	2	—	—
	Small-Before	4	2	2	16	3	2	—	2
	Acute	4	2	2	3	4	—	—	—
	Small-After	11	2	3	2	2	2	—	—
562	Small-Before	2	2	2	13	2	5	—	—
	Acute	2	2	2	2	2	2	—	—
	Small-After	18	2	2	2	4	4	4	—
586	Small-Before	3	3	2	21	2	6	5	—
	Acute	2	3	3	3	3	3	—	—
	Small-After	14	2	3	2	3	2	2	—
	Small-Before	2	2	2	14	2	2	4	—

^a Saline vehicle administered both before and after sessions.

home-cage and chamber conditions during repeated administration of a large dose.

Dose-response functions often were not assessed during repeated postsession testing with a large dose. As reported below, these conditions generally led to a cessation of key pecking. Hence we assumed that if no pecking followed the pre-session administration of saline that regularly occurred in the condition, tests with other, nonzero, doses would show the same thing. That supposition was confirmed in the three cases (Pigeons 33, 91, 393) in which dose-response functions were determined during repeated postsession administration of a large dose.

RESULTS

Because order of exposure played no discernible role in the main effects, the data are organized and presented by the three major repeated-dosing conditions.

Effects of Relatively Smaller Doses Administered Postsession

Although small doses were defined in part by the fact that they did not eliminate key pecking when given repeatedly after sessions, they did alter responding in some pigeons. Figure 1 shows data from the first and last 10 sessions of exposure to repeated postsession administration of a small dose. Response-rate decreases of about 40 to 60% in the FR 100 component occurred for Pigeons 32, 57, and 521, and rate was lowered occasionally in the FR 5 component for 586. These effects were not systematically related to whether the peak action of the drug occurred in the operant-conditioning chamber or in the home cage.

Figure 2 reveals that repeated postsession administration of a smaller dose generally resulted in tolerance. Six of the 7 pigeons showed clear shifts to the right in dose-response functions. In 5 of those 6 pigeons, curves were shifted to the right in both com-

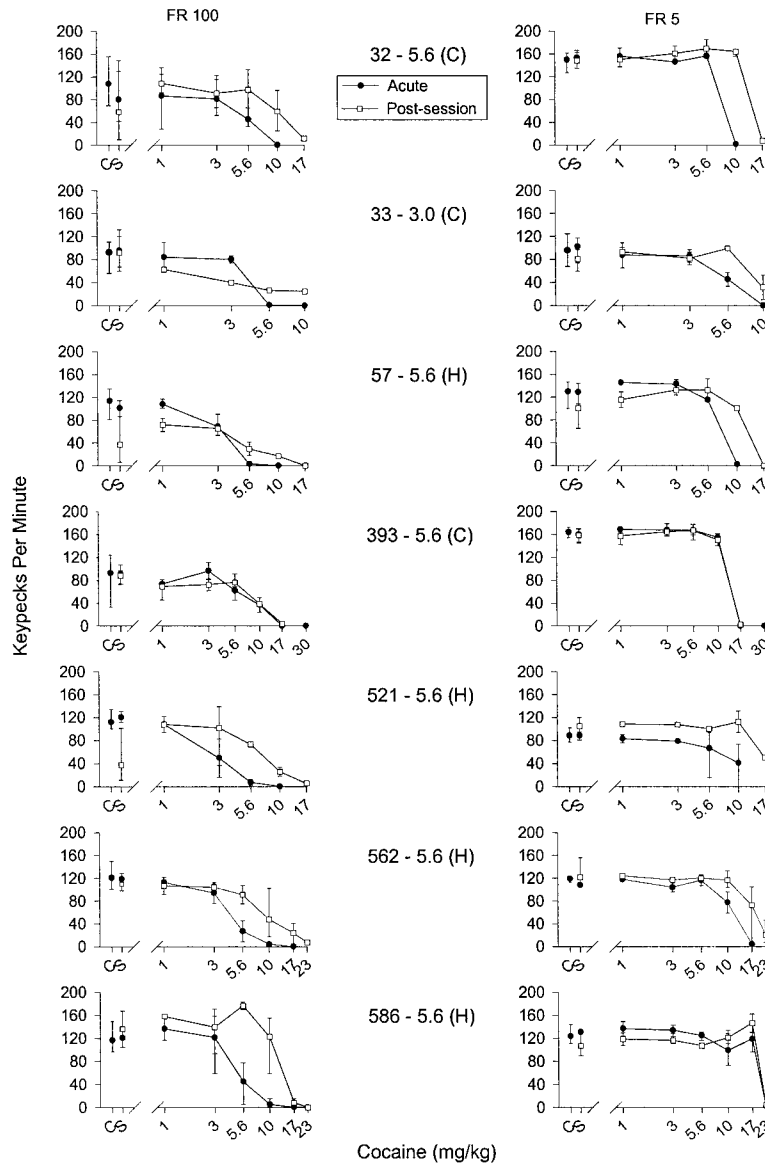


Fig. 2. Response rate as a function of dose of cocaine. Points are means of all administrations of each dose, and bars indicate ranges. If no bar is visible, the point covers the range. The points above C show means and ranges from all sessions that immediately preceded acute injections; those above S show means and ranges following administration of the saline vehicle before sessions that immediately preceded tests with pre-session doses of cocaine. Each row shows data for 1 pigeon, with that pigeon's identification number appearing between the graphs. Data in the left column are from the FR 100 component of the multiple schedule; those on the right are from the FR 5. Filled circles show effects of acute administrations, whereas open squares show effects after repeated exposure to post-session administration of a small dose of the drug. Next to each pigeon identification number is the dose given repeatedly. The letter in parentheses indicates whether the pigeon was returned to its home cage (H) or to the conditioning chamber (C) after receiving the drug. The functions for acute effects in Pigeons 33 and 393 are from a second assessment (see text).

exposure to postsession administration of the doses selected.

For 2 pigeons, 33 and 393, examinations of effects of small postsession doses came after those with larger doses. Before testing with smaller doses, therefore, baseline performance was reestablished in these 2 subjects, and dose-response determinations were conducted to ascertain if the prior experience with large doses had altered the functions. Because the dose-response functions had shifted slightly to the right, that is, modest tolerance was evident (data not shown), the new "acute" curves were used in subsequent comparisons for these 2 pigeons. For the remaining 5 pigeons exposed to this condition, effects of small doses were examined first, so their original acute dose-response curves served as the basis of comparisons.

Effects of Relatively Smaller Doses Administered Pre-session

Five pigeons were exposed to this condition immediately after completion of assessment of effects of postsession administration of the small dose. A 6th subject, Pigeon 32, did not experience the condition until after intervening exposure to three different post-session regimens with a large dose. Consequently, its dose-response function was redetermined before assessment of effects of pre-session administration of a small dose. The redetermination revealed little systematic change from the curve generated during repeated exposure to the small dose post-session (compare the open squares for this subject in Figures 2 and 3). Nevertheless, the more recent function was used in the comparisons, which are summarized for all 6 pigeons in Figure 3. The graphs in the left column reveal that curves for effects in the FR-100 component were not systematically altered. For Pigeon 562, baseline rates during FR 100 fell during this condition, but the form of the dose-response curve was generally unaffected. The functions in the right column, however, do show a change in several subjects. Under the FR 5 schedule, 3 pigeons, 33, 393, and 521, showed clear shifts in the functions indicative of tolerance. Specifically, rate decreases produced by large doses were attenuated. Pigeon 586 also showed a small effect in this component suggestive of tolerance. In these subjects, therefore, repeated

pre-session administration of cocaine resulted in additional tolerance that depended on the reinforcement schedule parameter. Also worthy of note is the effect of the repeatedly administered dose on behavior under the FR 5 schedule. The effects depicted in Figure 3 are representative of performance throughout the repeated-administration phase. That is, the dose was essentially without effect on performance. Nevertheless, additional tolerance was observed in some pigeons.

Effects of Relatively Large Doses Administered Post-session

When the dose given post-session was relatively large, the eventual result in most cases was that key pecking during the session was eliminated in both components of the multiple schedule. In a minority of cases, pecking was not eliminated, but its rate was reduced. These effects are illustrated in Figure 4, which shows rates from 10-session blocks. The blocks were selected to show periods of major transition in pecking rates. For example, the two graphs at the top of the figure show data from Pigeon 32. The left graph illustrates the transition from baseline levels of responding to nearly complete suppression in the home-cage condition. Key pecking ceased completely by the 18th session in the first exposure to this condition (filled circles, open squares), and by the 13th session in the second exposure (data not shown). In both exposures, rates in the large ratio decreased to zero before those in the small ratio. Following removal of post-session cocaine, responding recovered to baseline levels.

Similar results were obtained with Pigeon 32 in the chamber condition, as shown in the graph on the right. Post-session drug administration eventually resulted in complete suppression of key pecking and, as before, large-ratio performance decreased sooner than small-ratio responding. Also similar was the recovery of performance once the drug vehicle was substituted for cocaine.

The results for Pigeon 32 are generally characteristic of those of the other pigeons. Three exceptions are notable, however. First, for Pigeon 521, key pecking was reduced, but never completely eliminated, as a result of post-session administration of 10 mg/kg. The reduction was greater when drug administration was followed by a return to the condi-

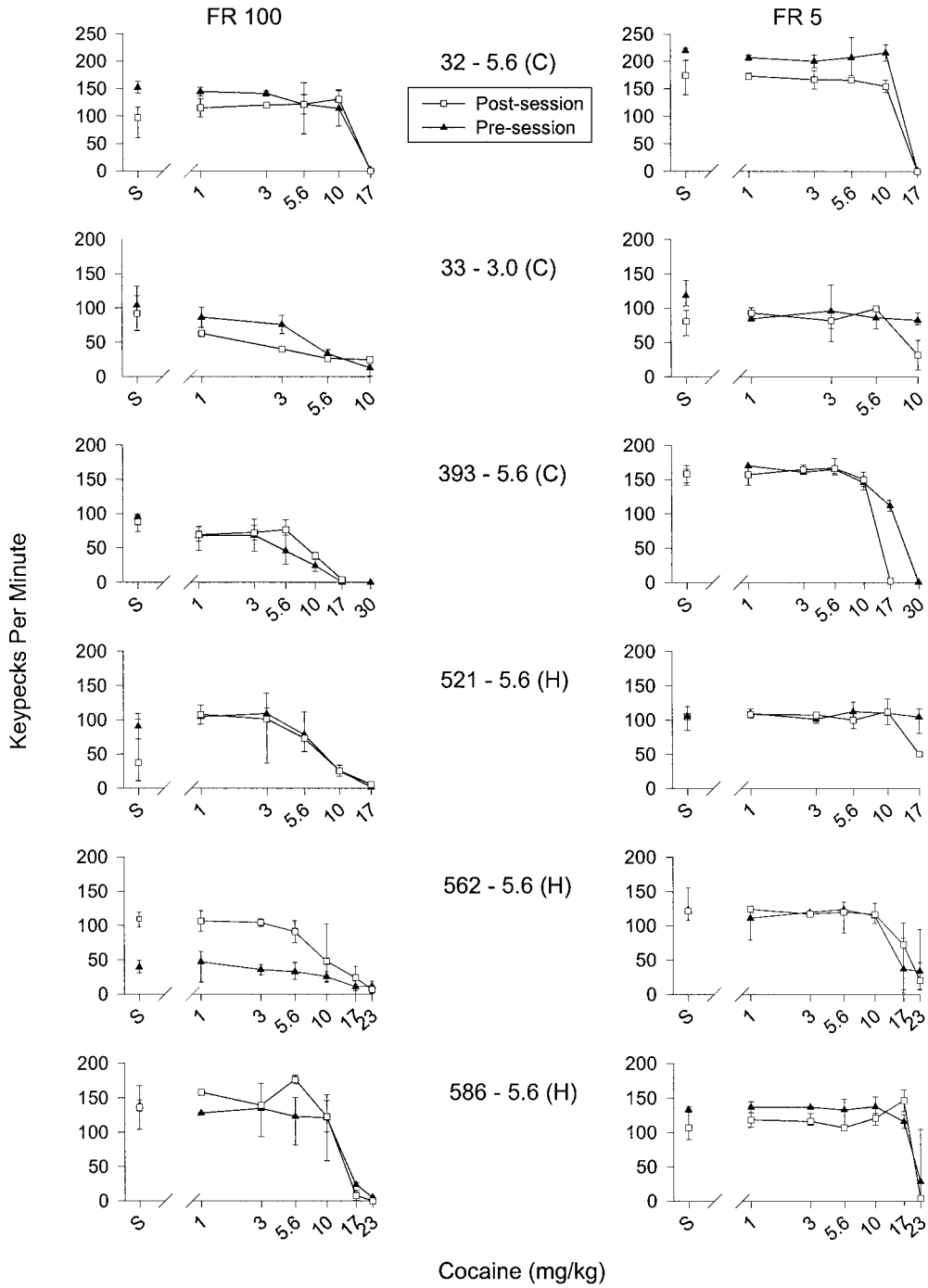


Fig. 3. Response rate as a function of dose of cocaine. Filled triangles show data following a period of repeated exposure to pre-session administration of a small dose of cocaine. Open squares are the data resulting after a period of repeated postsession administration of the same dose (i.e., they are the same data as the open squares in Figure 2, except for Pigeon 32; see text). Other details are as in Figure 2.

tioning chamber than when the pigeon was returned to its home cage, and rates during FR 100 were affected more than those in FR 5. Because pecking was not eliminated, the sessions displayed are the last 10 of the condition. The choice of the 10-mg/kg dose as large for this subject probably was not optimal. Tests with a large dose postsession were conducted relatively late in the sequence of conditions for this pigeon, and tolerance to effects of cocaine had developed such that 10 mg/kg given pre-session no longer completely eliminated key pecking, as it had originally.

The second exception to the general pattern of effects occurred in Pigeon 33 during its initial exposure to the home-cage condition (data not shown). This pigeon's key pecking did not cease in the 55 days of the condition. During Pigeon 33's second exposure to this condition, however, key pecking rate did reach zero as shown in the figure.

The third exception to the general pattern lies in the data of Pigeon 91 (fourth row, right column). For this subject, rate decreased to zero, but when postsession cocaine was replaced by saline, responding did not reoccur. After this failure, the subject was exposed to a variety of other manipulations (e.g., no injections, immediate return to the home cage, etc.), none of which resulted in the reemergence of key pecking. All told, this pigeon did not peck for nearly 300 sessions and was subsequently removed from the study.

The data in Table 3 support the view that behavior in the two multiple-schedule components was differentially sensitive to the rate-decreasing effects of postsession drug administration. The table shows the number of sessions before two successive sessions without pecks occurred. Responding in the FR 100 component decreased sooner than responding in the FR 5 component in 12 of the 13 instances in which complete suppression occurred. In the one exception (chamber condition for Subject 586), pecking ceased after the same number of sessions. This general finding held even when baseline rates were similar, as seen for Pigeons 33 and 562 (note overlap of points and ranges under control conditions in Figure 4), so the difference cannot reliably be attributed to differences in initial level of responding. The effect also was

unrelated to whether the home-cage or chamber condition was in effect.

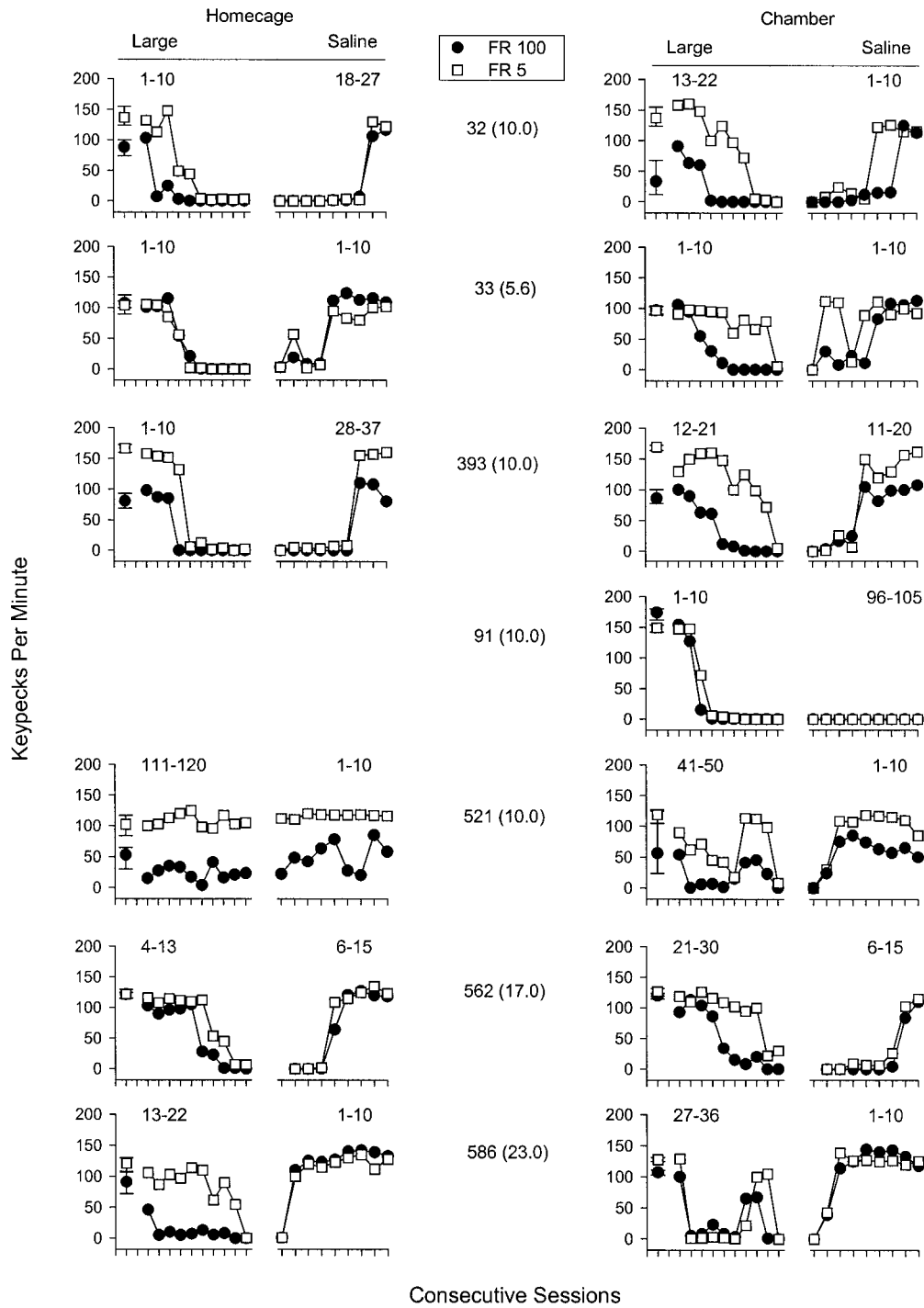
Once responding was absent in both components for two consecutive sessions, rates remained at zero for the rest of the condition. The number of consecutive sessions during which key pecking was absent in both components before postsession drug testing ended ranged from as few as eight (Pigeon 586, home-cage condition) to as many as 106 (Pigeon 33, chamber condition).

Although exposure to the chamber exerted no systematic effect on the likelihood of suppression in either of the two components of the multiple schedule, it was consistently correlated with how long it took suppression to develop in both components. In the 14 instances (seven for FR 5 and seven for FR 100) in which a within-subject comparison could be made, the data in Table 3 show that in no case was suppression slower to develop when a subject was returned to the home cage after the postsession drug injection. In only one, Pigeon 33 under FR 100, did it develop in the same number of sessions.

One might presume that suppression would develop first in the later portions of the session because these times were closer to that of drug administration. To assess this possibility, Figures 5 and 6 show response rates separately in the first, second, and third presentation of each component of the multiple schedule. Figure 5 shows data from the home-cage condition, Figure 6 those from the chamber condition. The sessions correspond to those in Figure 4. That is, in Figure 5, data from the 10 sessions over which responding declined in each left-column graph in Figure 4 have been expanded to show rates in each third of the session, and in Figure 6 the data from the right column have been expanded similarly. Figures 5 and 6 show clearly that the suppression did not first develop late in sessions and then spread to earlier times. Instead, when responding decreased it did so to an equal degree across the entire session. The data in Figures 5 and 6 also buttress those in Table 3 in indicating that responding in the FR 100 component generally disappeared before pecking in the FR 5 did.

DISCUSSION

The major findings of the present study were: (a) Relatively small doses of cocaine ad-



ministered repeatedly postsession generally resulted in the development of tolerance to the drug's response-rate reducing effects in both components of the multiple schedule; (b) relatively large doses administered after each session resulted in suppression of operant key pecking during sessions, an outcome that occurred whether or not the drug's peak action was experienced in the conditioning chamber or in the home cage; and (c) repeated pre-session administration of the small doses led to augmented tolerance in some pigeons, but these changes were limited to the small-ratio component of the multiple schedule. Each of these findings is discussed in order below.

An unexpected effect of repeated exposure to small doses of postsession cocaine was that it resulted in tolerance to the drug's rate-reducing effects, even though during the period of chronic exposure the drug's effects were not experienced while the FR contingencies were operative. That is, this tolerance was not contingent tolerance that depended on learning processes set in motion by experiencing the multiple-schedule contingencies while under the influence of drug, but rather must have been a result of other factors. What those factors might be, for example, changes in receptor affinity or altered metabolism, remain to be determined. That the effect was a general one is supported by the finding that tolerance was present to a roughly equivalent degree in both components of the multiple schedule.

The fact that tolerance developed when a small dose was given repeatedly after sessions is at odds with most of the literature on effects of postsession administration of stimulants, including cocaine (e.g., Branch & Sizemore, 1988; Smith, 1990). In his review of the literature on contingent tolerance, Wolgin

Table 3
Sessions to two consecutive sessions with a response rate of zero.

Subject	Condition	
	Home cage	Chamber
	FR 100/FR 5	FR 100/FR 5
32	7/18 (5/13) ^a	39/42
33	7/9	7/20 (8/13)
91	—	5/7
393	5/15	20/23
562	12/16	30/34
586	22/26	37/37

^a Numbers in parentheses are from replications.

(1989) noted that there were no reports of postsession administration of stimulants resulting in tolerance to behavioral effects, and we are not aware of any such reports published since his review. In fact, sensitization, not tolerance, has been reported to result from postsession administration of cocaine (Bowen et al., 1993; Woolverton et al., 1978). The present results, therefore, are apparently the first to document that tolerance to cocaine's effects on operant performance can result merely from repeated exposure to the drug.

Two differences between the present study and those that have reported contingent tolerance to effects of cocaine may account for our unusual findings. First, the subjects used here were pigeons, whereas earlier work has employed rats or nonhuman primates, so the outcome may reflect a species difference. Second, the behavioral procedures we used were relatively complex. We employed a multiple schedule, whereas most prior research has involved only a single contingency arrangement. Perhaps especially notable was the presence of the large FR schedule as one

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Fig. 4. Average response rate (pecks per minute) across selected blocks of 10 sessions during daily postsession administration of a large dose of cocaine or of the saline vehicle. The blocks of sessions were chosen to illustrate the periods when responding changed most extensively. The numbers above each block indicate the session numbers encompassed. Within each graph, the 10 connected points on the left are from sessions followed by injection of a large dose of cocaine, whereas those on the right are from the immediately following condition in which the drug vehicle, saline, was given after each session. Each row shows data from 1 pigeon, with that pigeon's identification number appearing between the graphs. In parentheses next to the identification number is the dose (in mg/kg), of cocaine designated as large for that subject. Graphs in the left column show data from sessions from the home-cage condition, whereas those in the right column display data from the chamber condition. Other details are as in Figure 1.

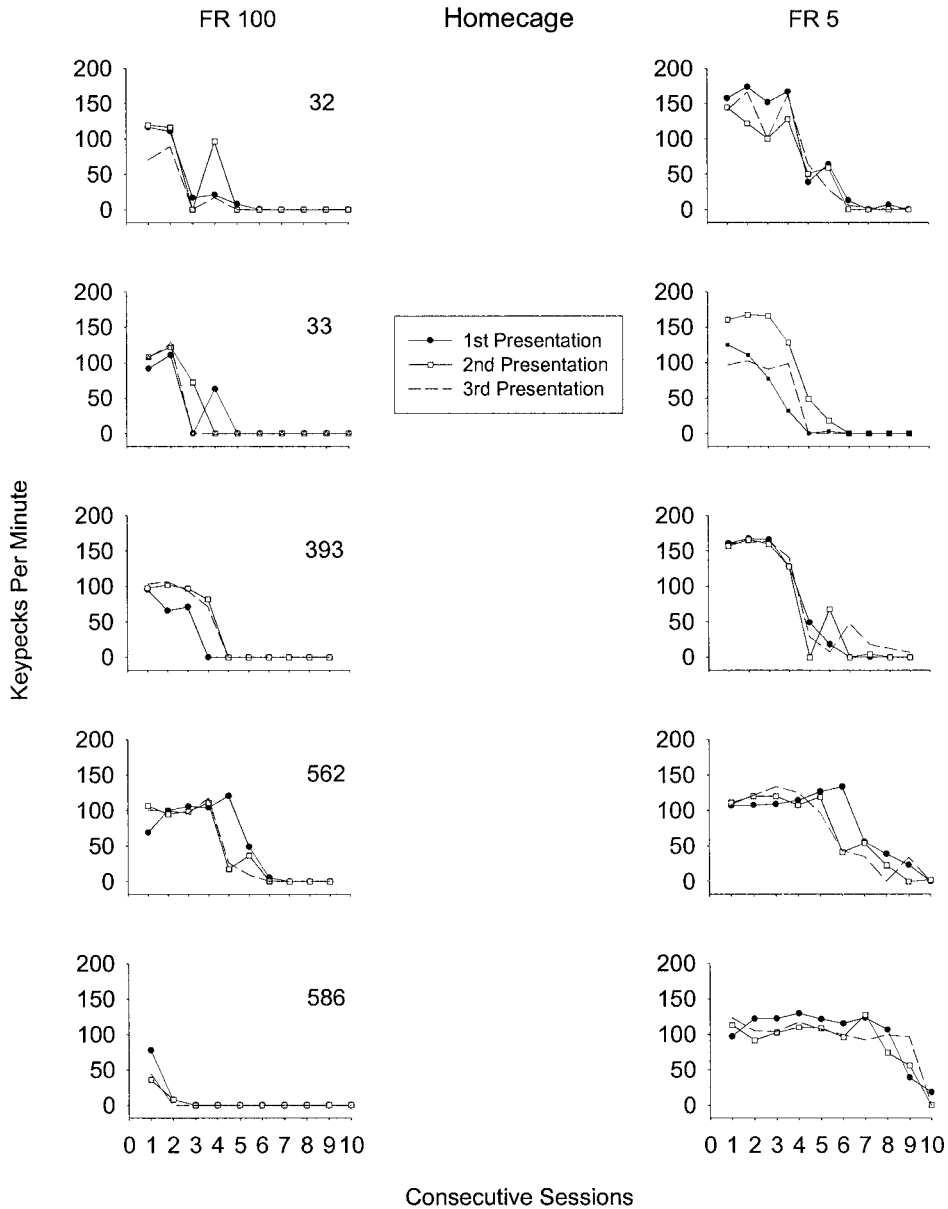


Fig. 5. Response rates across 10-session blocks, taken separately from the first, second, and third exposures to the two components of the multiple schedule within a session. Sessions were followed by administration of a large dose of cocaine, and data are from the same sessions as depicted in the left portions of the left column of Figure 4. That is, they are from the sessions in which suppression of pecking developed when postsession administration of a large dose of cocaine was followed immediately by a return to the home cage. Data from the FR 100 component are in the left column and those from the FR 5 are in the right. Each row shows data for 1 pigeon, with that pigeon's identification number shown in the left graph. Filled circles depict effects during the first presentation of the component, open squares depict those in the second presentation, and the dashed line shows those in the last presentation each session. Note that the functions do not differ systematically.

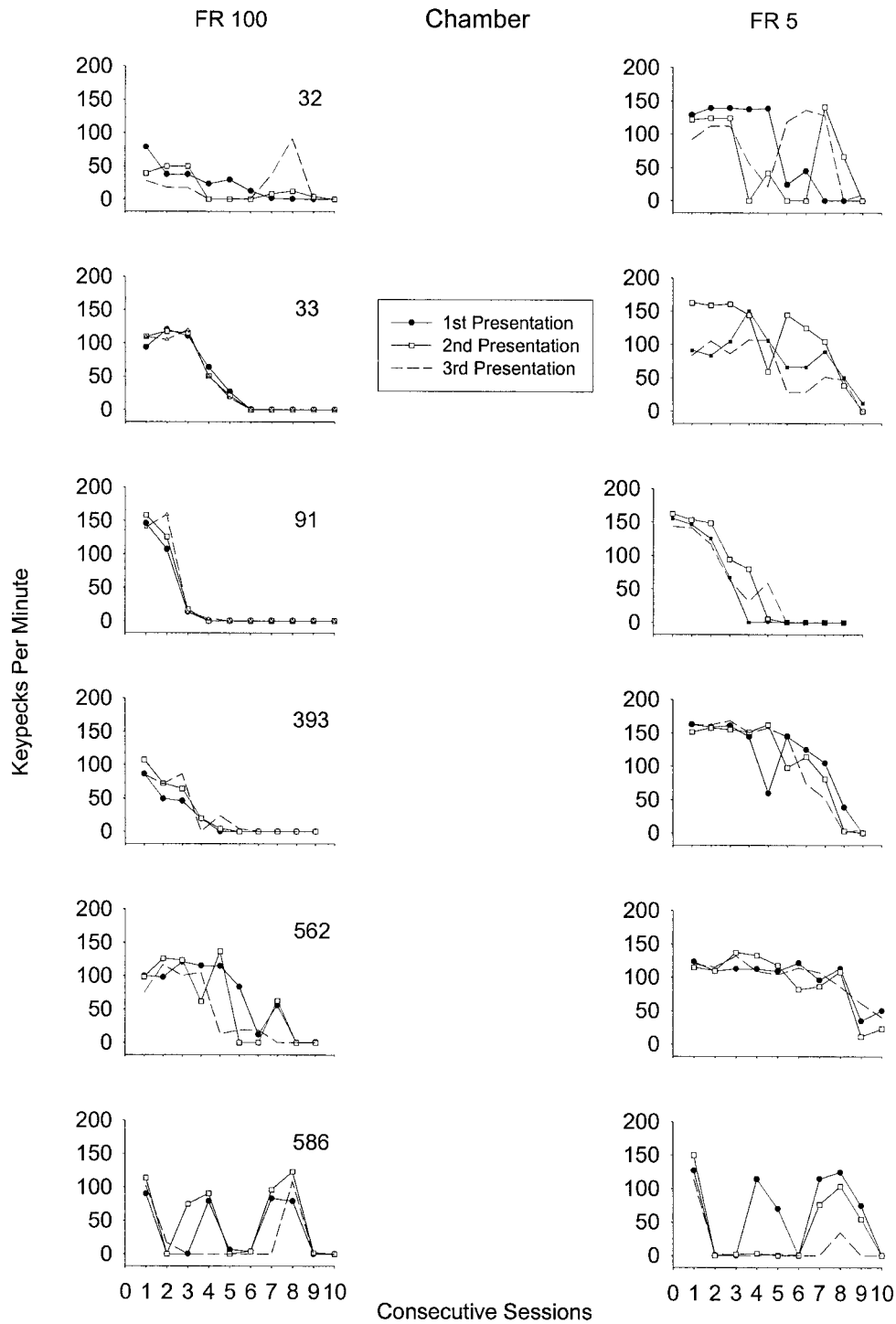


Fig. 6. Response rates from the first, second, and third exposures to the components of the multiple schedule, during the period of development of response suppression, for the sessions displayed in the graphs in the right column of Figure 4. The large ratio was FR 75 for Pigeon 91. Other details are as in Figure 5.

component of the multiple schedule. In previous research, response requirements have generally been of the type that can yield high rates of reinforcement (cf. Carlton & Wolgin, 1971; Smith, 1990), and in those circumstances contingent tolerance has consistently emerged. A test for the development of contingent tolerance in pigeons responding under simple, high-rate-of-reinforcement contingencies would help to illuminate whether the present observation of tolerance with postsession cocaine administration is based in species or in behavioral conditions.

Another difference between our research and earlier studies on effects of repeated exposure to postsession cocaine is that our periods of repeated administration were longer than those typically reported. Chronic exposure phases have frequently been on the order of 30 sessions or less (e.g., Carlton & Wolgin, 1971; Woolverton et al., 1978). In contrast, we exposed our subjects first to 60 sessions of postsession administration, and by the time dose-response analyses were complete the pigeons had had over 100 sessions of exposure (see Table 1). Additional research will be required to assess the role of number of postsession exposures to the drug.

With drugs other than cocaine, evidence of tolerance to effects on operant behavior emerging from postsession dosing has been reported. For example, Genovese, Elsmore, and Witkin (1988) found that postsession administration of physostigmine to rats responding under FR schedules resulted in tolerance. In contrast to the present research, however, they reported that tolerance occurred with a small FR, but not with a larger FR. That is, tolerance was schedule-parameter specific, which was not the case in the present experiments.

Repeated administration of large doses of postsession cocaine resulted in complete elimination of key pecking in all but 1 subject, Pigeon 521, and even that subject's behavior was decreased. Suppression occurred whether or not cocaine's action was paired with the chamber context or the home-cage context. The effect was also unrelated to the order of exposure to the various experimental conditions, testimony to its robustness.

When the drug vehicle, saline, was substituted for cocaine after suppression had developed, complete recovery of performance

was seen in all but one instance (for Pigeon 91, whose key pecking remained absent). This outcome is consistent with the view that the suppression was the result of a Pavlovian process. That is, when session-associated stimuli regularly preceded the administration of a large dose of cocaine, suppression developed. When cocaine administration was replaced by saline injections, the suppression abated. One interpretation of these effects is that the stimulus complex present in the session came to serve as a Pavlovian CS. Cocaine, at the dose given repeatedly, may have functioned as a Pavlovian US. The possibility that Pavlovian conditioning was evident is also supported by the fact that suppression occurred more rapidly in the FR 100 component than it did under the FR 5 schedule (See Table 3). Previous research on conditioned suppression, a phenomenon utilized to study Pavlovian conditioning (Domjan, 1996), has revealed that suppression is greater when reinforcement rate is lower (e.g., Blackman, 1968). The case for Pavlovian conditioning is not entirely clear, however, because no examination was conducted of effects of large doses of cocaine given independently of the session-related stimuli (cf. Rescorla, 1967), so it remains possible that the observed decreases in responding were the result of a generalized effect of prolonged exposure to repeated administration of a large dose.

The suppressive effect in the present study occurred whether the peak action of cocaine was experienced in the test chamber or in the home cage. No evidence, therefore, was generated to suggest that a CR that countered the effects of cocaine was produced by pairing the peak of drug action with the chamber context. Three features of our experimental design might have diminished the likelihood of observing development of a conditioned compensatory response when effects of postsession drug administration were paired with the experimental environment. First, the CS used for pairing was not identical to that present during the operant-conditioning sessions. During the latter, the key was illuminated, key pecking occurred, and food was presented. Of course, it is not possible to mimic every aspect of the conditioning situation during the period of postsession drug exposure, because to do so would require that the contin-

gencies of reinforcement be in effect. If they were, then mechanisms other than Pavlovian processes, for example, adjustments driven by reinforcement loss, could operate. Despite the limitation in degree of similarity between the actual operant session and the drug-pairing period, one might reasonably presume that having all the features of the conditioning chamber present, which is surely a distinctive environment for a pigeon, during the drug-pairing period would be sufficient to imbue the chamber-related stimuli with CS functions. Supporting this perspective are the data of Figures 5 and 6, which show that when suppression due to postsession drug administration was observed it occurred immediately from the beginning of the session onward. That is, the effect was evident before any key pecks or food presentations occurred, thus making it less likely that stimuli arising from them acted as a crucial part of a CS.

The second feature of the current experimental design that could have mitigated against the development of a compensatory conditioned response in the chamber conditions is that the pairing between the chamber and the drug's effects was intermittent. Each day that an operant session was conducted, pigeons in the chamber condition got to experience the putative CS, the chamber, once before the putative US, cocaine, and once while it exerted its peak effects. It is well known that intermittent pairing diminishes the effectiveness of classical conditioning procedures (see Mackintosh, 1974). It is also well established, nevertheless, that although intermittent pairing weakens Pavlovian conditioning, it does not prevent it. The data in Table 3 support the view that intermittent pairing slowed the development of conditioning. Suppression emerged more slowly when the pigeons were returned to the chamber after each session, which resulted in two exposures per day to the putative CS, one of which preceded drug administration, and the other which overlapped with the drug's action.

A third possibility is that the chamber condition can be construed as incorporating a mixture of forward and backwards pairings, whereas the home-cage condition involved only forward pairing. Perhaps the backwards pairings of the chamber condition slowed the effectiveness of the forward pairings.

Other research has also shown that session-related stimuli paired with postsession drug administration can result in suppression of operant performance (Glowa & Barrett, 1983; Logue, 1980). Glowa and Barrett, for example, exposed pigeons responding on an FR schedule to stimuli correlated with postsession administration of various doses of *d*-amphetamine across conditions. When the colors of lights in the food hopper reliably signaled postsession amphetamine, response rate during the session was decreased in a dose-dependent manner. Small doses produced small decreases, whereas larger doses eliminated key pecking, a pattern of effects similar to that seen here. Their pigeons, when rates were decreased, showed lower rates later in sessions, whereas the decreases were session-wide in the current study. Glowa and Barrett had sessions that were not followed by drug interspersed among those that were, and that may account for the differences in within-session patterns of responding between the two studies.

The temporal separation of the onsets of the putative conditional and unconditional stimuli in the present study reveals the maintenance of conditioned suppression of responding by large postsession doses to be consistent with the literature on conditioned flavor aversions (cf. Rozin & Kalat, 1971). Cocaine administration occurred 20 min after the end of a session. Additionally, when key pecking was suppressed, sessions lasted nearly 1.5 hr. Thus almost 2 hr intervened between session onset and administration of cocaine, yet pecking was suppressed immediately at the beginning of each session and remained so throughout. It is noteworthy, too, that suppression was evident throughout the session from the very beginning of its development (Figures 5 and 6). Thus, if the Pavlovian-conditioning interpretation of this effect is correct, it implies that pairing a US, cocaine, with a serial CS, session-related stimuli followed by handling and holding-cage stimuli, can result in maintenance of conditioning even though the delay from CS onset to US onset is on the order of 2 hr. The fact that suppression developed with a long delay between putative CS onset and cocaine delivery suggests that this outcome might be considered a reflection of reinforcer devaluation (cf. Adams & Dickinson, 1981; Colwill & Res-

corla, 1985). That is, grain might have become less effective as reinforcement as a result of its consumption, at least during the development of suppression, preceding the administration of cocaine. The reinforcer devaluation procedure developed by Adams and Dickinson is based on the phenomenon of conditioned flavor aversion in that a reinforcer is devalued by pairing it with the subsequent administration of a drug (lithium chloride in their experiments).

Apparent Pavlovian conditioning with long delays when cocaine serves as the US has also been reported by Goudie, Dickins, and Thornton (1978). They showed that when a novel saccharin flavor was paired with large doses of cocaine (e.g., 20 and 36 mg/kg) in rats, subsequent intake of the solution was decreased when cocaine administration was delayed for as long as 90 min after drinking. Our results are consistent with the view that large doses of cocaine can be effective as USs with long delays between CS and US and extend that effect to operant performance beyond that involved in the immediate consumption of food or liquid.

In contrast to the effects of repeated post-session administration of a small dose of cocaine, pre-session administration of the same dose produced tolerance that was evident only in performance under the small FR (in some subjects). In this regard, the present results systematically replicate those of Hoffman et al. (1987), Nickel et al. (1993), and van Haaren and Anderson (1994) who also found that repeated pre-session administration of cocaine resulted in tolerance to effects on behavior controlled by a small FR, but not on those to responding engendered by a relatively large FR. Our finding, however, was limited to only 3 of the 6 pigeons exposed to this condition, with a hint in a 4th pigeon. It is important to recall, however, that all the subjects had been exposed previously to repeated post-session dosing that had resulted in tolerance. Thus any changes wrought by pre-session dosing had to augment tolerance that had already developed. Branch et al. (2000) have noted the difficulty in enhancing tolerance to effects of cocaine on FR performance once it has been established, so it is somewhat notable that additional tolerance could be obtained in any of the subjects by

moving the drug administration from after sessions to before.

The additional tolerance observed in the FR 5 component appeared only after drug administration was moved from after each session to before each session, and therefore qualifies as an instance of contingent tolerance. The present procedures, therefore, resulted in the development of tolerance when the small dose was given after sessions, and also in contingent tolerance when that dose was given before sessions. Contingent tolerance, however, was limited to the small fixed ratio. Most reports of contingent tolerance with cocaine have used relatively small response requirements (e.g., Branch & Sizemore, 1988; Smith, 1990), so the finding of contingent tolerance in the small ratio again suggests that investigation of the role of response requirement in the development of contingent tolerance could be fruitful.

A puzzling feature of the present results from pre-session drug administration, however, is that tolerance developed in the FR 5 component even though no loss of reinforcement was produced by the repeatedly administered dose. Inspection of the dose-response curves in Figure 3 (open squares, right column) shows that the dose given before each session produced no noticeable change in overall response rate, and therefore no change in reinforcement rate. Normally, it has been assumed that contingent tolerance depends on a behavioral adjustment to a loss of reinforcement (See Wolgin, 1989). Such a process could not have operated in the present study, so our result is an instance of tolerance that meets the definition of contingent tolerance, but for which the usual account does not apply.

One possibility is that the additional tolerance that developed in the FR 5 component was simply the result of ever more exposure to cocaine. Although that possibility cannot be ruled out fully, features of the procedure and data argue against it. First, we designed our dose-response assessments so that we could detect any systematic shifts in the functions while they were being determined, and no such shifts were seen. Dose-response determinations took at least 10 weeks to complete, so ample opportunity to see systematic changes over prolonged drug exposure existed. Second, the overall experimental design

resulted in what in essence is a multiple baseline across subjects, an approach widely used to study irreversible changes in individual subjects (Baer, Wolf, & Risley, 1968; Barlow & Hersen, 1984). The 3 subjects in which additional tolerance was seen with pre-session dosing, therefore, had markedly different behavioral and drug histories before the pre-session dosing began. Tables 1 and 2 reveal that they differed on how long they had been exposed to the behavioral and drug procedures, with Pigeon 33 having been exposed to hundreds more sessions than had Pigeons 393 and 521. They also differed on how many prior injections of cocaine they had experienced with 521 having experienced 141 drug administrations, 393 having had 326, and 33 having had 376 injections before daily pre-session drug administration began.

To summarize, the present experiments revealed that repeated postsession administration of relatively small doses of cocaine resulted in the development of tolerance in both components of the multiple schedule, an effect that was not expected, and one that suggests purely pharmacological variables were responsible for the changes in the drug's effect. Giving the same small dose consistently before each session resulted in additional tolerance (in some pigeons) in the small-FR component of the multiple schedule, but not the large-FR component, thus implicating behavioral factors. Repeated postsession administration of relatively large doses of cocaine resulted in suppression of responding during sessions, an effect that was consistent with an account based on Pavlovian conditioning. None of these results was systematically related to whether the pigeons spent a postsession period in the conditioning chamber or in their home cages, nor did they depend on the order in which conditions were experienced.

REFERENCES

- Adams, C. D., & Dickinson, A. (1981). Instrumental responding following reinforcer devaluation. *Quarterly Journal of Experimental Psychology*, *33B*, 109–121.
- Adams, W. J., Yeh, S. Y., Woods, L. A., & Mitchell, C. L. (1969). Drug-test interaction as a factor in the development of tolerance to the analgesic effect of morphine. *Journal of Pharmacology and Experimental Therapeutics*, *168*, 251–257.
- Baer, D. M., Wolf, M. M., & Risley, T. R. (1968). Some current dimensions of applied behavior analysis. *Journal of Applied Behavior Analysis*, *1*, 91–97.
- Barlow, D. H., & Hersen, M. (1984). *Single-case experimental design: Strategies for studying behavior change* (2nd ed.). New York: Pergamon Press.
- Blackman, D. E. (1968). Response rate, reinforcement frequency, and conditioned suppression. *Journal of the Experimental Analysis of Behavior*, *11*, 503–516.
- Bowen, S. E., Fowler, S. C., & Kallman, M. J. (1993). Effects of variation in chronic dose of cocaine on contingent tolerance as assessed in a milk-drinking task. *Psychopharmacology*, *113*, 67–75.
- Branch, M. N., & Sizemore, G. M. (1988). Behavioral tolerance to cocaine in squirrel monkeys: Acute and chronic effects on complex operant behavior. *Pharmacology, Biochemistry, & Behavior*, *30*, 737–748.
- Branch, M. N., Wilhelm, M. J., & Pinkston, J. W. (2000). A comparison of fixed and variable doses of cocaine in producing and augmenting tolerance to its effects on schedule-controlled behavior. *Behavioural Pharmacology*, *11*, 555–569.
- Brown, P. L., & Jenkins, H. M. (1968). Autoshaping of the pigeon's key peck. *Journal of the Experimental Analysis of Behavior*, *11*, 1–8.
- Carlton, P. L., & Wolgin, D. L. (1971). Contingent tolerance to the anorexigenic effects of amphetamine. *Physiology & Behavior*, *7*, 221–223.
- Chen, C. S. (1968). A study of the alcohol-tolerance effect and an introduction of a new behavioural technique. *Psychopharmacologia*, *12*, 433–440.
- Colwill, R. M., & Rescorla, R. A. (1985). Postconditioning devaluation of a reinforcer affects instrumental responding. *Journal of Experimental Psychology: Animal Behavior Processes*, *11*, 120–132.
- Domjan, M. (1996). *The essentials of conditioning and learning*. Pacific Grove, CA: Brooks/Cole Publishing.
- Downs, A. W., & Eddy, N. B. (1932a). The effect of repeated doses of cocaine on the dog. *Journal of Pharmacology and Experimental Therapeutics*, *46*, 195–198.
- Downs, A. W., & Eddy, N. B. (1932b). The effect of repeated doses of cocaine on the rat. *Journal of Pharmacology and Experimental Therapeutics*, *46*, 199–200.
- Genovese, R. F., Elsmore, T. F., & Witkin, J. M. (1988). Environmental influences on the development of tolerance to the effects of physostigmine on schedule-controlled behavior. *Psychopharmacology*, *96*, 462–467.
- Glowa, J. R., & Barrett, J. E. (1983). Response suppression by visual stimuli paired with postsession *d*-amphetamine injections in the pigeon. *Journal of the Experimental Analysis of Behavior*, *39*, 165–173.
- Goudie, A. J., Dickens, D. W., & Thornton, E. W. (1978). Cocaine-induced conditioned taste aversions in rats. *Pharmacology, Biochemistry, & Behavior*, *8*, 757–761.
- Hoffman, S. H., Branch, M. N., & Sizemore, G. M. (1987). Cocaine tolerance: Acute versus chronic effects as dependent upon fixed-ratio size. *Journal of the Experimental Analysis of Behavior*, *47*, 363–376.
- Hughes, C. E., & Branch, M. N. (1991). Tolerance to and residual effects of cocaine in squirrel monkeys depend on reinforcement-schedule parameter. *Journal of the Experimental Analysis of Behavior*, *56*, 345–360.
- Logue, A. W. (1980). Visual cues for illness-induced aversions in the pigeon. *Behavioral and Neural Biology*, *28*, 372–373.
- Mackintosh, N. J. (1974). *The psychology of animal learning*. London: Academic Press.

- Mercier, J. J., & Déssaigne, S. (1960). Détermination de l'accoutumance expérimental par une méthode psychophysologique: Étude de quelques drogues sympathomimétiques et de la cocaïne. *Annales Pharmaceutiques Françaises*, *18*, 502–518.
- Moore, M. S., & Thompson, D. M. (1978). Acute and chronic effects of cocaine on extinction-induced aggression. *Journal of the Experimental Analysis of Behavior*, *29*, 309–318.
- Nickel, M., Alling, K., & Poling, A. (1993). Fixed-ratio size as a determinant of tolerance to cocaine: Is relative or absolute size important? *Behavioural Pharmacology*, *4*, 471–478.
- Palya, W. L., & Walter, D. E. (1993). A powerful, inexpensive experiment controller or IBM PC interface and experiment control language. *Behavior Research Methods, Instruments, & Computers*, *25*, 127–136.
- Post, R. M., & Rose, H. (1976). Increasing effects of repetitive cocaine administration in the rat. *Nature*, *260*, 731–732.
- Post, R. M., Weiss, S. R. B., Fontana, D., & Pert, A. (1992). Conditioned sensitization to the psychomotor stimulant cocaine. *Annals of the New York Academy of Sciences*, *654*, 386–399.
- Rescorla, R. A. (1967). Pavlovian conditioning and its proper control procedures. *Psychological Review*, *74*, 71–80.
- Rozin, P., & Kalat, J. W. (1971). Specific hungers and poison avoidance as adaptive specializations of learning. *Psychological Review*, *78*, 459–486.
- Schuster, C. R., Dockens, W. S., & Woods, J. H. (1966). Behavioral variables affecting the development of amphetamine tolerance. *Psychopharmacologia*, *9*, 170–182.
- Siegel, S. (1978). Tolerance to the hyperthermic effect of morphine in the rat is a learned response. *Journal of Comparative & Physiological Psychology*, *92*, 1137–1149.
- Siegel, S., Baptista, M. A. S., Kim, J. A., McDonald, R. V., & Weise-Kelly, L. (2000). Pavlovian psychopharmacology: The associative basis of tolerance. *Experimental & Clinical Psychopharmacology*, *8*, 276–293.
- Smith, J. B. (1986). Effects of chronically administered *d*-amphetamine on spaced responding maintained under multiple and single-component schedules. *Psychopharmacology (Berl)*, *88*, 296–300.
- Smith, J. B. (1990). Situational specificity of tolerance to decreased operant responding by cocaine. *Pharmacology, Biochemistry, & Behavior*, *36*, 473–477.
- Stafford, D., & Branch, M. N. (1996). Relations between dose magnitude, subject sensitivity, and the development of tolerance to cocaine-induced behavioral disruptions in pigeons. *Behavioural Pharmacology*, *7*, 324–333.
- Stewart, J., & Badiani, A. (1993). Tolerance and sensitization to the behavioral effects of drugs. *Behavioural Pharmacology*, *4*, 289–312.
- van Haaren, F., & Anderson, K. G. (1994). Behavioral effects of acute and chronic cocaine administration in male and female rats: Effects of fixed-ratio schedule parameters. *Behavioural Pharmacology*, *6*, 607–614.
- Wolgin, D. L. (1989). The role of instrumental learning in behavioral tolerance to drugs. In A. J. Goudie & M. W. Emmett-Oglesby (Eds.), *Psychoactive drugs: Tolerance and sensitization* (pp. 17–114). Clifton, NJ: Humana Press.
- Woolverton, W. L., Kandel, D., & Schuster, C. R. (1978). Tolerance and cross tolerance to cocaine and *d*-amphetamine. *Journal of Pharmacology and Experimental Therapeutics*, *205*, 525–535.

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